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Alcohol-Related Liver Disease Is Rarely Detected at Early Stages Compared With Liver Diseases of Other Etiologies Worldwide

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BACKGROUND & AIMS: **Despite recent advances in treatment of viral hepatitis, liver-related mortality is high, possibly owing to the large burden of advanced alcohol-related liver disease (ALD). We investigated whether patients with ALD are initially seen at later stages of disease development than patients with hepatitis C virus (HCV) infection or other etiologies.**

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Abbreviations used in this paper: ALD, alcohol-related liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

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METHODS: **We performed a cross-sectional study of 3453 consecutive patients with either early or advanced liver disease (1699 patients with early and 1754 with advanced liver disease) seen at 17 tertiary care liver or gastrointestinal units worldwide, from August 2015 through March 2017. We collected anthropometric, etiology, and clinical information, as well as and model for end-stage liver disease scores. We used unconditional logistic regression to estimate the odds ratios for evaluation at late stages of the disease progression.**

RESULTS: **Of the patients analyzed, 81% had 1 etiology of liver disease and 17% had 2 etiologies of liver disease. Of patients seen at early stages for a single etiology, 31% had HCV infection, 21% had hepatitis B virus infection, and 17% had nonalcoholic fatty liver disease, whereas only 3.8% had ALD. In contrast, 29% of patients seen for advanced disease had ALD. Patients with ALD were more likely to be seen at specialized centers, with advanced-stage disease, compared with patients with HCV-associated liver disease (odds ratio, 14.1; 95% CI, 10.5–18.9; $P < .001$). Of patients with 2 etiologies of liver disease, excess alcohol use was associated with 50% of cases. These patients had significantly more visits to health care providers, with more advanced disease, compared with patients without excess alcohol use. The mean model for end-stage liver disease score for patients with advanced ALD (score, 16) was higher than for patients with advanced liver disease not associated with excess alcohol use (score, 13) ($P < .01$).**

CONCLUSIONS: **In a cross-sectional analysis of patients with liver disease worldwide, we found that patients with ALD are seen with more advanced-stage disease than patients with HCV-associated liver disease. Of patients with 2 etiologies of liver disease, excess alcohol use was associated with 50% of cases. Early detection and referral programs are needed for patients with ALD worldwide.**

Keywords: NAFLD; Mortality; Cirrhosis.

In 2015, chronic liver diseases were responsible for 2% of worldwide mortality.[1] The main causes of cirrhosis are hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as alcohol-related and nonalcoholic fatty liver disease (ALD and NAFLD, respectively). Increased research attention in the past few decades has resulted in advances for viral hepatitis, with the subsequent development of highly effective all-oral therapies. Today, interest from the research community has spiked for NAFLD.[2] In contrast, less than 4% of the research attention in hepatology is devoted to ALD, despite its burden.[3] According to the World Health Organization, ALD is responsible for 50% of cases of cirrhosis worldwide. [4] ALD is also the second most common indication for liver transplant in the United States.[5]

Most chronic liver diseases have a silent course until the development of complications. For patients with compensated disease, the presence of significant liver fibrosis predicts decompensated disease and early mortality.[6] Therefore, diagnosis at early stages is imperative to prevent liver-related morbidity and mortality. Patients with HBV or HCV routinely are identified early with widely available serologic tests before the development of decompensated liver disease. Similarly, increasing efforts are underway to detect NAFLD in its early forms using laboratory and imaging analysis in patients with obesity and metabolic syndrome. In contrast, there are few programs for early diagnosis of ALD. Many patients with alcohol use disorders are not detected in routine clinical practices and most centers do not use noninvasive tools to detect liver fibrosis in this particular high-risk patient population.[7,8] With the introduction of early accurate detection and intervention, the economic and health burden of ALD can be prevented.

To date, there are no specific studies that have assessed disparities in the etiology of liver disease among patients with early or compensated liver disease vs those with advanced liver disease. This study examined the possibility of such disparities at a global level by including centers from 5 continents. Furthermore, we investigated geographic differences of the etiologies of both early and late liver disease on a global scale.

Methods

Design, Setting, and Participants

This was an international, observational, multicenter investigation with retrospectively identified patients referred with both early and advanced liver disease. Seventeen liver or gastrointestinal units across 5 continents participated in the study (Supplementary Figure 1). Our aim was to investigate the disparities of the major liver disease etiologies between early and late medical visits at specialized centers, and whether those differences may be better explained by the

etiology itself or by confounding factors. Data were collected from the last encounter for patients referred with suspected current liver disease. Data were gathered from the time of admission (cross-sectional). One hundred consecutive patients with early liver disease were included from an outpatient setting. One hundred consecutive patients with advanced liver disease were included from an inpatient setting. (Figure 1 and Supplementary Methods section).

Patient Selection and Definitions

A total of 3453 patients were included in the study. Definitions of advanced and early liver disease are described in Figure 1. Diagnostic criteria to define the etiology of the liver disease are listed in Supplementary Table 1. The following were required for each etiology. For HBV, a positive DNA, HBV surface antigen positivity, or chronic suppression with an antiviral agent was required. For HCV, a positive RNA by a sensitive molecular method or a clinical history of a previous cure for at-risk patients. For ALD, a consumption of 60 g/d or more for men and 40 g/d or more for women for at least 6 months were required along with a body mass index of less than 30. For NAFLD, compatible findings were required along with a body mass index greater than 35 and/or the presence of diabetes, dyslipidemia, the exclusion of secondary causes, and a maximum daily alcohol consumption of 30 g for men and 20 g for women. Autoimmune hepatitis was diagnosed with positive autoantibodies and histologic confirmation or a score of 7 or greater according to the simplified diagnostic criteria of the International Autoimmune Hepatitis Group. Primary biliary cholangitis was confirmed with the presence of antimitochondrial antibodies (>1:40), increased alkaline phosphatase levels, and biopsy-proven disease. The diagnoses of primary sclerosing cholangitis required the exclusion of other cholestatic disorders and compatible radiographic findings and/or histologic confirmation. A Wilson disease scoring system of 4 or greater confirmed the diagnosis of

What You Need to Know

Background

We performed a multinational cross-sectional study to determine whether patients with alcohol-associated liver disease (ALD) are initially evaluated at later stages of disease development than patients with hepatitis C virus–associated liver disease or other etiologies.

Findings

Of patients evaluated with early stage liver disease, only 3.8% had ALD. In contrast, 29% of patients evaluated for advanced disease had ALD. Patients with ALD were more than 14-fold more likely to be evaluated at specialized centers, with advanced-stage disease, compared with patients with hepatitis C virus–associated liver disease.

Implications for patient care

Early detection and referral programs are needed for patients with ALD worldwide.

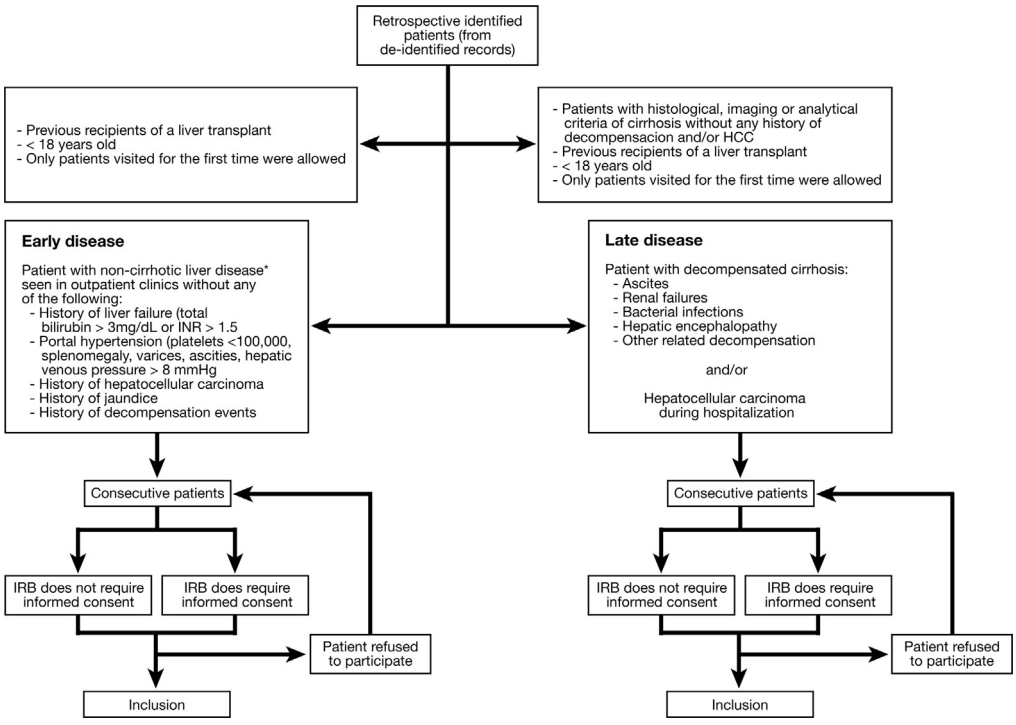

Figure 1. Flow chart of included patients and characteristics of each group. *Patients with no evidence of cirrhosis (F4), assessed either by liver biopsy or noninvasive tests. HCC, hepatocellular carcinoma; INR, international normalized ratio; IRB, institutional review board.

Table 1. General Characteristics of the Whole Series and Likelihood of Having a Medical Visited at Advanced vs Early Stages Compared With HCV

	Early N = 1699	Advanced N = 1754	*P* value	Bivariable analysis	
				OR (95% CI)	OR *P* value
Age, median (IQR), *y*	50 (39–59)	58 (50–66)	<.001		
≤40, n (%)	502 (29.5)	175 (10)	<.001	0.2 (0.16–0.25)	<.001
41–50, n (%)	384 (22.6)	285 (16.2)		0.38 (0.31–0.47)	<.001
>50, n (%)	813 (47.9)	1294 (73.8)		1 (reference)	
Sex, n (%)					
Female	762 (44.8)	582 (33.2)	<.001	0.61 (0.53–0.7)	<.001
Male	937 (55.2)	1172 (66.8)		1 (reference)	
Race, n (%)					
Asian	326 (19.2)	290 (16.5)	>.05	—	
Black	147 (8.7)	139 (7.9)		—	
Hispanic	17 (1)	13 (0.7)		—	
Indeterminate[a]	177 (10.4)	199 (11.3)		—	
Indian	117 (6.9)	118 (6.7)		—	
Middle Eastern	154 (9.1)	167(9.5)		—	
Other	14 (0.8)	11 (0.6)		—	
White	747 (44)	817 (46.6)		—	
Etiology, n (%)					
HCV	527 (31)	298 (17)	<.001	1 (reference)	
HBV	362 (21.3)	161 (9.2)		0.78 (0.62–0.99)	.004
ALD	64 (3.8)	509 (29)		14.1 (10.5–18.9)	<.001
NAFLD	287 (16.9)	120 (6.8)		0.74 (0.57–0.96)	.02
Cryptogenic	50 (2.9)	98 (5.6)		3.5 (2.4–5)	<.001
AIH	64 (3.8)	53 (3)	>.05	1.5 (0.99–2.7)	.06
PBC	32 (1.9)	13 (0.7)	.004	0.72 (0.37–1.4)	.3
PSC	14 (0.8)	14 (0.8)	>.05	1.8 (0.83–3.8)	.14
DILI	19 (1.1)	12 (0.7)		1.1 (0.5–2.3)	.8
HFE	20 (1.2)	1 (0.1)	<.001	0.09 (0.01–0.66)	.018
Wilson	5 (0.3)	2 (0.1)	>.05	—	
Schistosomiasis	3 (0.32)	6 (0.3)		—	
Other alone	26 (1.5)	33 (1.9)		2.2 (1.3–3.8)	.003
HCV and ALD	32 (1.9)	102 (5.8)	<.001	5.6 (3.7–8.6)	<.001
HBV and ALD	10 (0.6)	37 (2.1)	<.001	6.5 (3.2–13.3)	<.001
NAFLD and ALD	27 (1.6)	77 (4.4)	<.001	5 (3.2–7.9)	<.001
Other combinations	104 (48.6)	124 (32.6)	<.001	2.1 (1.5–2.8)	<.001
HCV and NAFLD	41 (2.4)	40 (2.3)	>.05	1.72 (1.1–2.7)	.02
Triple etiologies	11 (0.6)	49 (2.8)	<.001	7.88 (4–15.4)	<.001
Quadruple etiologies	1 (0.1)	5 (0.3)	>.05	8.8 (1–76)	.05

AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; HFE, hemochromatosis; IQR, interquartile range; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.
[a]Indeterminate race or ethnicity including mixed race population.

this disease. Drug-induced liver injury was a diagnosis of exclusion based primarily on a detailed history of blood tests, hepatobiliary imaging, and a liver biopsy, along with a history of recent exposure to a hepatotoxic agent. Hemochromatosis diagnosed was performed according to the more recent guidelines. Finally, those patients were declared as having an unclear cause of liver disease after performing a physical examination and extensive laboratory, imaging, and histologic evaluation.

Cases were collected from August 2015 until March 2017. All data were uploaded into a web-based system developed by the Center for Gastrointestinal Biology and Disease from the University of North Carolina at Chapel Hill.

Statistical Analysis

The chi-squared test was used to compare frequency distributions between subgroups for categoric variables. The Mann–Whitney *U* test was used to compare continuous variables when variables did not follow normal distributions. Unconditional logistic regression was used to estimate the odds ratios (ORs) for having a medical visit at a specialist center at a late stage of the disease, including age at visit, sex, and etiology. For each variable, we estimated the crude (unadjusted) OR for a visit at a late stage. We then performed multivariable logistic regression to estimate the ORs, adjusting for potential confounding variables (Supplementary Methods section).

Results

General Characteristics

A total of 3453 patients were included in the study; 1699 patients with early liver disease and 1754 with advanced liver disease. General characteristics are listed in Table 1, and Supplementary Figures 2 and 3. The majority of patients were white (45.3%), followed by Asian patients (17.8%). The most common single etiologies in the whole series were HCV (23.9%), ALD (16.6%), HBV (15.1%), and NAFLD (11.8%). Importantly, 2 or more etiologies were seen in 19.1% of patients. Patients with early medical visits to a specialized center were younger (50 vs 58 y; $P < .001$) and more likely to be female (44.8% vs 33.2%; $P < .001$) compared with patients with advanced-stage visits. Within the entire cohort, including patients with single and multiple etiologies, patients with viral hepatitis and NAFLD had medical visits during early stages of the disease, whereas patients with ALD predominately had medical visits during advanced stages of the disease (Table 1).

Patients With a Single Etiology of Liver Disease

A total of 2793 patients had a single etiology of liver disease. The most common etiologies for this cohort of patients were HCV (29.5%), ALD (20.5%), HBV (18.7%), and NAFLD (14.6%). Importantly, patients with HBV and NAFLD were less likely to have medical visits at late stages compared with HCV (OR, 0.78; 95% CI, 0.62–0.99; $P = .004$ and OR, 0.74; 95% CI, 0.57–0.96; $P = .02$, respectively) (Figure 2, Supplementary Table 2). Although ALD was the second most common cause of liver disease with 573 patients, only 11% were seen at early stages, whereas the majority were seen at advanced stages (OR, 10.4; 95% CI, 8–13.7; $P = .001$) compared with HCV patients. These results indicate that ALD is by far the most common disease that is detected at later stages when patients require hospitalization owing to liver-related complications.

We then assessed differences in the presentation and/or severity among patients with advanced disease. Patients with ALD (n = 509) presented with 1255 liver-related complications (2.5 complications per patient), whereas non-ALD patients (n = 811) presented with 1552 complications (1.9 complications per patient; $P < .01$ comparing ALD vs non-ALD patients). Hepatic encephalopathy, upper gastrointestinal bleeding, and ascites were present in 38.9%, 34.8%, and 80.6% of advanced ALD patients, respectively. Complications were less frequent in all of the other liver etiologies with the exception of NAFLD, which showed hepatic encephalopathy in 39.1% of cases. ALD patients presented with a higher percentage of complications and more severe liver disease compared with other etiologies, as assessed by a higher model for end stage liver disease score (median, 16 vs 13, respectively; $P < .01$) (Table 2).

Patients With Multiple Etiologies of Liver Disease

A total of 660 patients presented with multiple etiologies of liver disease. Most patients had 2 etiologies, whereas only 1.9% of patients had more than 2 etiologies. For patients with double etiologies, HCV-ALD represented 22.6%, NAFLD-ALD represented 17.5%, HCV-NAFLD represented 13.6%, HBV-ALD represented 7.9%, and other combinations represented 38.4%. All patients with double etiologies had higher percentages of advanced-stage visits with the exception of cases with HCV-NAFLD. The likelihood of medical visits at advanced vs early stages compared with HCV for HCV-ALD, NAFLD-ALD, and HBV-ALD were higher (OR, 5.6; 95% CI, 3.7–8.6; OR, 5; 95% CI, 3.2–7.9; and OR, 6.5; 95% CI, 3.2–13.3; $P < .001$, respectively). Interestingly, the sole etiology combination that did not involve alcohol, HCV-NAFLD, had the same number of patient visits at early and late stages (Figure 3 and Supplementary Table 2). Our results indicate that alcohol is the main co-factor in patients with liver disease worldwide. Alcohol increases the incidence of specialized medical visits with advanced disease owing to decompensation (Supplementary Figure 4). In fact, patients with double etiologies involving ALD presented at a higher percentage of decompensations compared with patients with double etiologies without ALD (Table 2).

Geographic Differences

We sought to identify differences in the etiology and specialized centers' medical visits of patients with liver diseases according to geographic location. Results of the ORs of advanced vs early visits compared with HCV for both single and multiple etiologies by continent is shown as a heatmap in Figure 4. The most frequent etiology in Africa, America, Asia (all countries), and Europe was HCV, whereas in Oceania it was ALD. Of note, the fact that patients with early ALD did not have medical visits at gastrointestinal/liver centers implies that this etiology was under-represented in the whole series (Supplementary Table 3).

In America, the main etiology of liver disease was HCV (25.5%), followed by ALD (13.8%) and NAFLD (12.6%). ALD patients presented at advanced stages (OR, 23.8; 95% CI, 8–35; $P < .001$). Remarkably, although obesity-associated NAFLD is highly prevalent in the United States, and active campaigns exist for early detection, patients were seen equally at both early (n = 49) and severe (n = 52) disease stages. Furthermore, in American patients with double etiologies, alcohol was present in almost two thirds of cases (Supplementary Table 5).

Table 2. Characteristics of Patients With Advanced Liver Disease

	HCV N = 298	HBV N = 161	ALD[a] N = 509	NAFLD N = 120	Cryptogenic N = 98	AIH N = 53	Other[b] N = 81
Inpatients, n (%)							
First admission	133 (44.6)[c]	63 (39.1)	185 (36.3)	43 (35.8)	33 (33.7)	13 (24.5)	25 (30.8)
Re-admission	165 (55.3)[c]	98 (60.9)	324 (63.7)	77 (64.2)	65 (66.3)	40 (75.5)	56 (69.2)
Decompensations, n (%)							
HE	78 (26.2)[c]	32 (19.9)[c]	198 (38.9)	47 (39.1)	24 (24.5)[c]	13 (24.5)	19 (23.5)[c]
UGIB	76 (25.5)[c]	42 (26)[c]	177 (34.8)	35 (29.2)	29 (29.6)	13 (24.5)	20 (24.6)
Ascites	178 (59.7)[c]	82 (50.9)[c]	410 (80.6)	81 (67.5)[c]	71 (72.4)	28 (52.8)[c]	47 (58)[c]
Jaundice	116 (38.9)[c]	54 (33.5)[c]	274 (53.8)	39 (32.5)[c]	40 (50)	16 (30.2)[c]	40 (60.5)
HCC early/advance	16 (5.4)[c]/30 (10)[c]	8 (4.7)[c]/27 (16.7)[c]	6 (1.2)/29 (5.7)	4 (3.3)/6 (5)	3 (3)/5 (5.1)	1 (1.9)/2 (3.8)	0/1 (1.2)
HRS	26 (8.7)	14 (8.7)	62 (12)	15 (12.5)	11 (11.2)	10 (18.9)	0
HPS	3 (1)	0	1 (0.2)	0	2 (2)	1 (1.9)	0
SBP or sepsis	66 (22)[c]	17 (10.6)	82 (16)	27 (22.5)	6 (6.1)[c]	12 (22.6)	19 (23.5)
MELD, median (IQR)	13 (9.8–17)[c]	13 (8.2–19)[c]	16 (12–22)	13 (10–20.7)[c]	14.5 (9–20.3)[c]	12 (8–14)[c]	14 (10–19)[c]

	Double etiologies involving ALD N = 278	Double etiologies without ALD N = 102	3 and 4 etiologies N = 54
Inpatients, n (%)			
First admission	74 (26.6)[c]	25 (24.5)[c]	11 (20.3)[c]
Re-admission	204 (73.4)[c]	77 (75.5)[c]	43 (79.6)[c]
Decompensations, n (%)			
HE	131 (47.1)[c]	31 (30.4)	25 (46.3)
UGIB	88 (31.7)	29 (28.4)	13 (24.1)
Ascites	191 (68.7)[c]	55 (53.9)[c]	31 (57.4)[c]
Jaundice	110 (39.6)[c]	43 (42.2)[c]	10 (18.5)[c]
HCC early/advance	4 (1.4)/24 (8.6)	1 (0.9)/7 (6.9)	1 (1.9)/1 (1.9)
HRS	26 (9.4)	8 (7.8)	3 (5.6)
HPS	1 (0.4)	0	0
SBP or sepsis	71 (25.5)[c]	17 (16.7)	10 (18.5)
MELD, median (IQR)	13 (9.5–18)[c]	13 (10–18)[c]	11 (20.3)[c]

HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HPS, hepatopulmonary syndrome; HRS, hepatorenal syndrome; IQR, interquartile range; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis; UGIB, upper gastrointestinal bleeding.

[a]Reference category.

[b]Because of their low global frequency PSC, primary biliary cholangitis, DILI, hemochromatosis, Wilson disease, other etiologies, and schistosomiasis have been grouped with the etiology of *other*.

[c]$P < .05$.

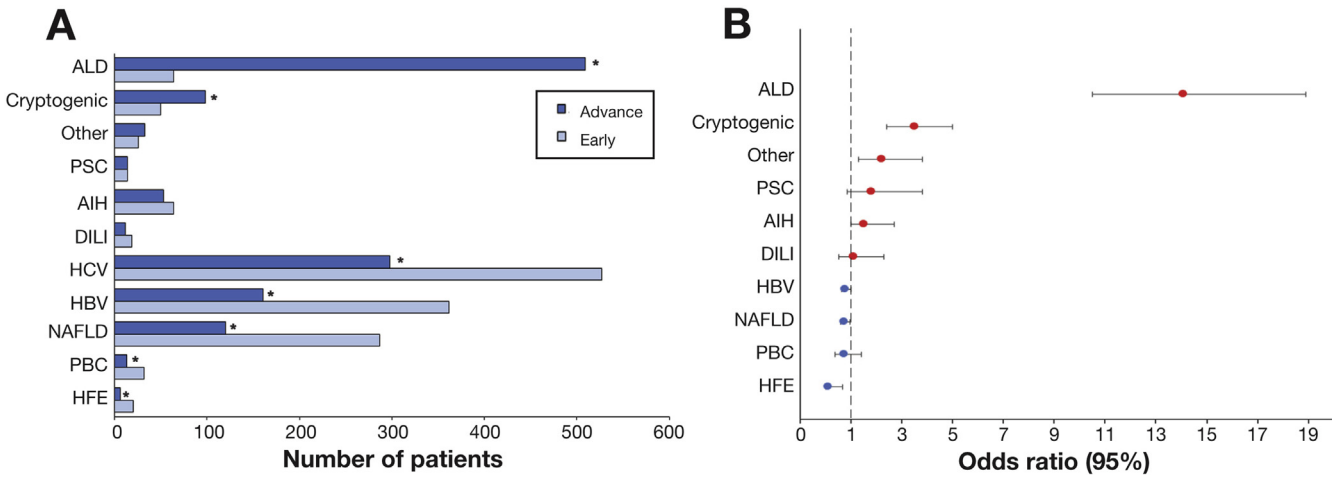

Figure 2. Medical visits at specialized centers of patients with a single etiology. (*A*) Number of patients with medical visits at advanced vs early liver stages. *$P < .05$. (*B*) Odds ratio of being seen at an advanced stage. AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; HFE, hemochromatosis; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

The main etiology of liver disease in Europe was HCV (19.4%), followed by ALD (17.5%) and HBV (10.8%), and NAFLD only accounted for 9% of cases. Although HBV and NAFLD showed ORs of 0.6, 95% CI of 0.3 to 1.1, and a *P* value of .008, and an OR of 0.62, 95% CI of 0.34 to 0.13, and a *P* value of .1, respectively, ALD presented with an alarming OR of 51.7, 95% CI of 24 to 108, and a *P* value of .001 toward late specialized centers' medical visits in comparison with HCV patients. Interestingly, up to 15.2% of European patients presented with double etiologies involving ALD. This group of patients had an advanced to early OR of 10.3, 95% CI of 6.3 to 16.7, and a *P* value less than .001 (Figure 4, Supplementary Table 4).

In our African cohort, HCV (35%) was the main etiology of liver disease, probably reflecting a low number of patients from sub-Saharan regions, followed by HBV (14%), ALD (18.8%), and cryptogenic causes (15%). Although most patients with viral hepatitis received an early diagnosis, the late/early detection fold ratios did not reach statistical significance (0.88 for HCV and 0.6 for HBV patients, respectively). The OR for ALD patients was 1.9, with a 95% CI of 1.1 to 3.4, and a *P* value of 03, the lowest value across all continents. Of note, the total number of patients seen with ALD was low compared with the other continents (Supplementary Table 4).

The main etiology of liver disease in Asia was HCV (24.8%), followed closely by HBV (22.4%), NAFLD (18.2%), and, finally, ALD (15.2%). South Korea and China's main etiology of disease was HBV. In contrast, the main etiology in Kuwait was HCV, ALD in India, and both HCV and ALD shared the first position in Singapore. Ten percent of Asian patients presented with double etiologies, of which 60% involved ALD. The Asian population ORs for advanced vs early medical visits for ALD was 10.3, the 95% CI was 6 to 17.8, and the *P* value was less than .001 compared with HCV patients. Because of the geographic and ethnic diversity of this continent, we performed a country-by-country analysis (Supplementary Table 5).

Oceania is only represented by 1 country (Australia). ALD was the main etiology (26%), followed by HBV (19.5%) and HCV (14%). HBV is seen more frequently at late stages, with an OR of 1.5, a 95% CI of 0.42 to 5.8, and a *P* value of .5, whereas ALD had a remarkable OR of 306, a 95% CI of 32 to 2886, and a *P* value of less than .001 compared with HCV patients. Patients with double etiologies involving ALD also presented an outstanding OR of 30, a 95% CI of 7.2 to 125, and a *P* value of less than .001 (Figure 4, Supplementary Table 4).

All of the statistically significant ORs remained significant when we performed the multivariate analysis including age and sex (Supplementary Table 4). This geographic analysis showed that a lack of specialized centers' medical visits by patients with early forms of ALD is a constant finding across all continents.

Because the most striking finding of our study was the global-wide delay in specialized center visits by patients with ALD, we analyzed those differences based on age, sex, and race, as shown in Supplementary Tables 6, 7, 8, and 9.

Discussion

With the development of highly effective all-oral drugs and the existence of reliable serologic markers, great advances have been made in the early diagnosis and therapy of viral hepatitis.[9,10] Similarly, the worldwide epidemic of obesity has increased awareness of NAFLD.[11] In clear contrast, few advances have been made in the diagnosis and management of patients with ALD.[12] In our clinical experience, many patients with early forms of viral hepatitis and NAFLD are referred to specialized centers, whereas ALD patients are rarely

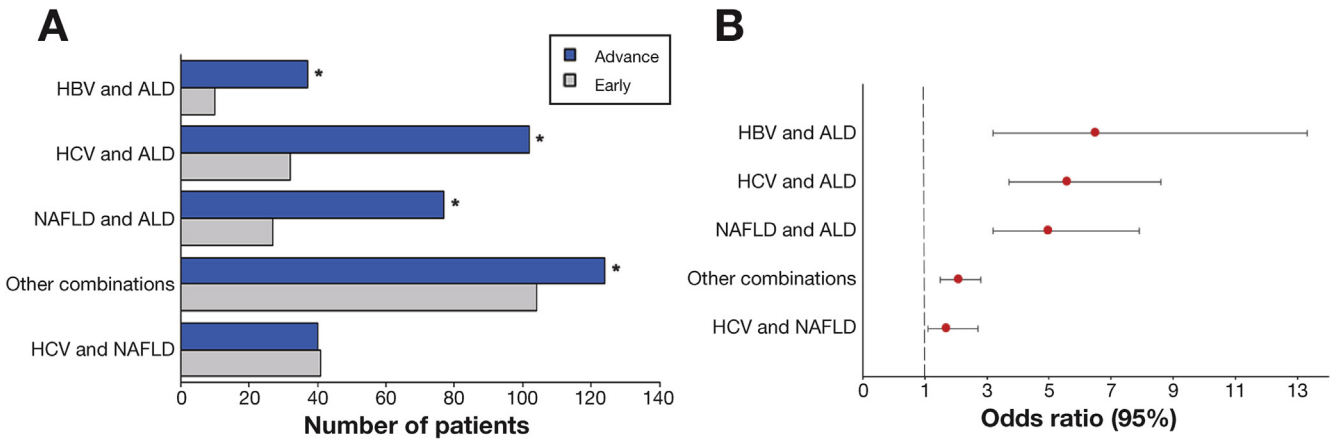

Figure 3. Medical visits at specialized centers by patients with double etiologies. (*A*) Number of patients with medical visits at advanced vs early liver stages. *$P < .05$. (*B*) Odds ratio of being seen at advanced stage vs early liver disease stages. ALD, alcohol-related liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease.

detected at early stages. To test this hypothesis, we performed a worldwide study including countries from 5 continents to investigate differences regarding medical visits of early vs advanced disease to specialized centers of patients with different types of liver diseases.

We used different strategies to minimize the risk of bias. First, we included 17 different liver/gastroenterology centers from 5 continents and included 100 consecutive patients regardless of liver disease etiology. We also included patients with multiple etiologies to offer a complete picture of real-life scenarios, however, it is important to note that cryptogenic etiology may represent burned-out NAFLD. Finally, we included 2 clearly different disease stages: early disease (ie, patients without evidence of cirrhosis and without any previous known liver-related decompensation) and advanced disease (ie, patients with decompensated cirrhosis or hepatocellular carcinoma that required hospitalization). Because the prognosis of patients with compensated/silent cirrhosis is uncertain and the life expectancy can be long,[13,14] patients with compensated cirrhosis without any previous decompensation were not included in our study.

The most represented etiologies in the entire cohort were viral hepatitis (39%), followed by ALD (16.6%). Because patients with early ALD were not referred to specialized centers across all nations, this population clearly was under-represented in the whole cohort. Although we detected widespread geographic differences, ALD was the only etiology with a negative early/advanced specialized center medical visit ratio across all 5 continents.

The advanced/early ORs for ALD compared with HCV in the entire cohort was 14.1, with an alarming 306 and 51.7 in Oceania and Europe, respectively. These results strongly indicate that medical visits of ALD patients at early stages is almost nonexistent. This data also are supported by Shoreibah et al,[15] who showed that ALD patients were more likely to present at advanced stages compared with NAFLD patients.

Patients with early ALD are seen mostly in drug or alcohol addiction clinics and typically are not referred to gastrointestinal/liver specialists until they have developed a decompensating event. Therefore, primary care centers, drug and alcohol clinics, and the liver community should focus efforts on developing early detection programs in patients with alcohol use disorders, such as noninvasive testing for significant liver fibrosis (ie, elastography).[8] Other strategies, such as universal screening for alcohol misuse in acute medical admission, have been proposed to detect early ALD.[16] Other efforts should focus on the design of quality clinical trials to assess the efficacy of different treatments (ie, intestinal decontamination) on alcohol use and fibrosis reversibility. It also is highly recommended that patients with significant fibrosis be referred to tertiary care centers.

Another remarkable finding of our study was that alcohol was the main co-factor in patients with double etiologies and increased the chances patients were referred to the hospital at advanced stages. Patients with advanced disease and double etiologies with ALD presented with a higher percentage of decompensations compared with patients with double etiologies without ALD. This fact reinforces the idea that alcohol intake can impact the initiation and progression of chronic liver diseases regardless of the origin. This important finding highlights the need for screening of alcohol abuse (ie, Alcohol Use Disorder Identification Test questionnaire) in all patients with liver disease regardless of the suspected etiology.[7,17] It is critical to identify these patients and refer them to specialist centers with both hepatology and addiction experts.[18] It is important to highlight that patients with ALD can develop a unique entity called *alcoholic hepatitis* characterized by an abrupt and rapid increase in bilirubin level, with increased liver enzyme levels, arising in the background of heavy alcohol use that might play a role in those patients presenting with more severe liver disease.

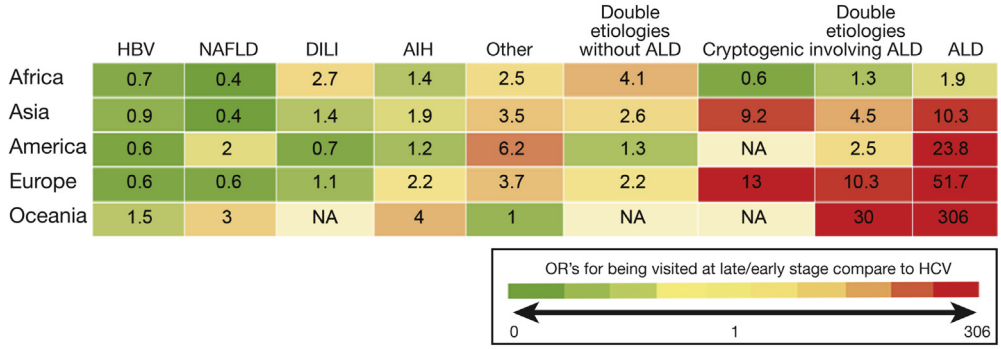

Figure 4. Heatmap expression of the likelihood of having a medical visit at advanced vs early stages compared with HCV by continent. Red color shows those etiologies with the highest likelihood of being seen at advanced vs early stages of liver disease compared with HCV and green color shows the contrary. Because of their low global frequency, Wilson disease, hemochromatosis, schistosomiasis, and triple or quadruple etiologies were grouped with the category of *other*. AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; DILI, drug-induced liver injury; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

This study had several limitations. The most important is the retrospective nature of the study, because data were collected retrospectively from the last encounter with a patient, which can lead to inaccuracies in the etiology of liver disease for a patient. Nevertheless, centers were required to carefully assess the existence of alcohol abuse to label patients with ALD. Moreover, it is possible that some patients with alcohol addiction were referred to gastrointestinal/liver specialists but did not show up to the visit or self-referred to the emergency department during later stages of the disease. Unfortunately, we did not record that information. Multiple reasons can explain this finding, including the lack of early detection, lack of referral, and the stigma around alcohol use disorder, which leads to increased social rejection, negative emotions, and structural discrimination. Interventions need to be made to address all of these issues and further studies should be designed specifically to address all of these questions.[18] Although we made considerable efforts to include a representative number of countries from each continent, Africa (with 2 centers) and Oceania (with 1 center) were underrepresented. This might lead to a selection bias in these continents. The results from these regions should be confirmed in larger studies. The other continents were represented by at least 4 centers, which offers a more accurate picture, but the risk of selection bias still exists. Finally, this study was performed by tertiary care centers, which may see a disproportionate volume of patients with advanced disease compared with general hospitals. Moreover, some of the race/ethnicity groups clearly are under-represented even in the most ethnically diverse countries (ie, Hispanics).

In conclusion, there are significant worldwide disparities in patients with liver disease who visit specialized centers. Patients with ALD are rarely seen at early stages in specialized care centers compared with patients with viral etiologies of hepatitis and NAFLD. Alcohol also is the main co-factor of liver disease and increases the risk of having the first specialized medical visit at a late stage. Programs aimed at early identification and specialized centers' medical visits of ALD are urgently needed at a global level.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.01.026.

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Conflicts of interest
The authors disclose no conflicts.

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Supplementary Methods

Design, Setting, and Participants

Advanced liver disease patients were included independently of whether the patients were admitted through the emergency department, direct admission to the hospital, or transfer from a nonspecialist center. The centers recruited for the study were required to be academic or tertiary care centers that specialized in the care of liver patients. To provide a global assessment of liver disease, centers were chosen in each of the major World Health Organization regions to account for regional or geographic variations of liver disease. All centers specialized in the care of general hepatology patients and did not have specific subspecialization with the exception of 1 center in Russia. Two centers, 1 from Bosnia and Herzegovina and 1 from Russia, included 199 and 254 patients, respectively, owing to methodologic or facilities idiosyncrasies (see Supplementary Figure 1 for further explanations). All local Ethics Committees approved the study design, methodologies, and end points. Written informed consent was obtained from patients before data acquisition when required by the local Ethics Committee. Each center entered data into a de-identified, web-based Health Insurance Portability and Accountability Act–compatible database system.

Patient Selection and Definitions

Cases with early liver disease were defined as patients with no evidence of cirrhosis (F4), assessed either by liver biopsy or noninvasive tests. This cohort included patients with noncirrhotic liver disease seen exclusively in outpatient clinics without any of the following: history of liver failure (total bilirubin level $>$ 3 mg/dL or international normalized ratio $>$ 1.5), portal hypertension (platelets $<$ 100,000, splenomegaly, varices, ascites, hepatic venous pressure gradient $>$ 8 mm Hg), history of hepatocellular carcinoma, history of jaundice, or history of decompensating events. Most of the patients were referred to centers from nonspecialist clinics and primary care centers by either general practitioners, internal medicine physicians, or general gastroenterologists. Cases with advanced liver disease were defined as patients with decompensated cirrhosis (eg, ascites, renal failure, bacterial infections, jaundice, or encephalopathy) and/or hepatocellular carcinoma requiring hospitalization for a liver-related episode. Patients with histologic, imaging, or analytic criteria of cirrhosis but without any history of decompensations and/or hepatocellular carcinoma were not included in this study. Exclusion criteria for both early and advanced patients included age younger than 18 years and a history of liver transplantation. The vast majority of patients were new referrals, transferred from other centers, or were never seen previously by a hepatologist/gastroenterologist. Patients were allowed to have 2 or more potential etiologies of liver disease. If no cause of liver disease was identified, the patient was labeled as *cryptogenic*. When liver disease was attributable to uncommon causes not included in the database, each center was asked to elaborate the etiology in a free-text field. Anthropometric data included year of birth, sex, and patient self-identified race. Races included (in alphabetic order): Asian, black, Hispanic, indeterminate or mixed races, Indian subcontinent, Middle Eastern, and white. This classification was predefined by the investigators. For patients with early liver disease, data regarding the encounter (initial medical visit or follow-up evaluation) were collected. For patients with advanced liver disease, specific encounter information was collected regarding hospital admission to a unit and first hospitalization or re-admission. Clinical data were collected for advanced-stage patients regarding history of decompensating events or complications of chronic liver disease. The model for end-stage liver disease score at the time of the encounter also was included, if available.

Statistics Analysis

Results are presented as frequencies and percentages, means and SDs for normal continuous variables, and median and quartile 1 and 3 for non-normal continuous variables.

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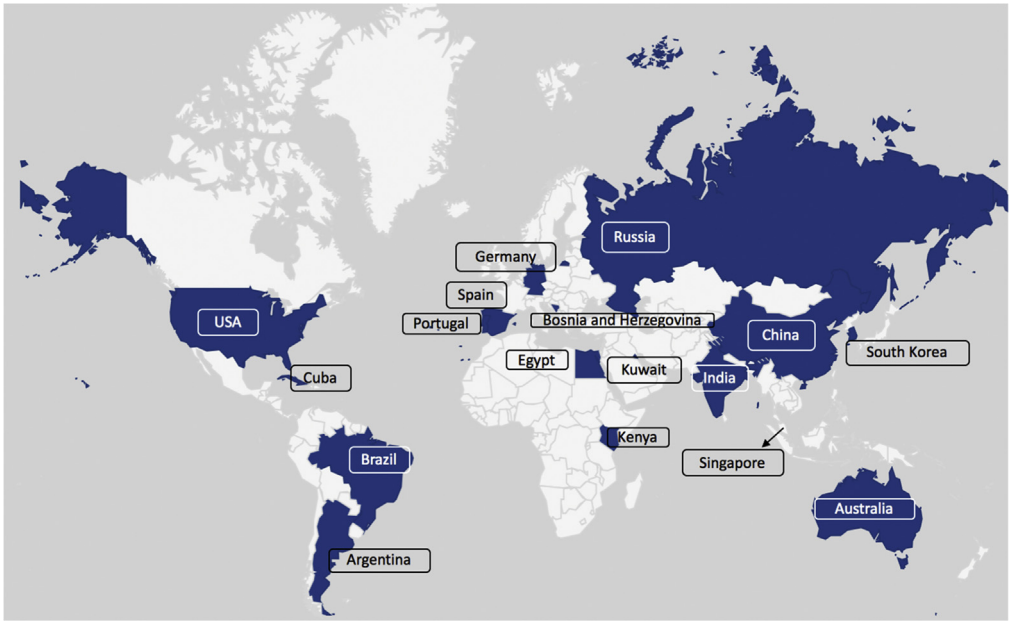
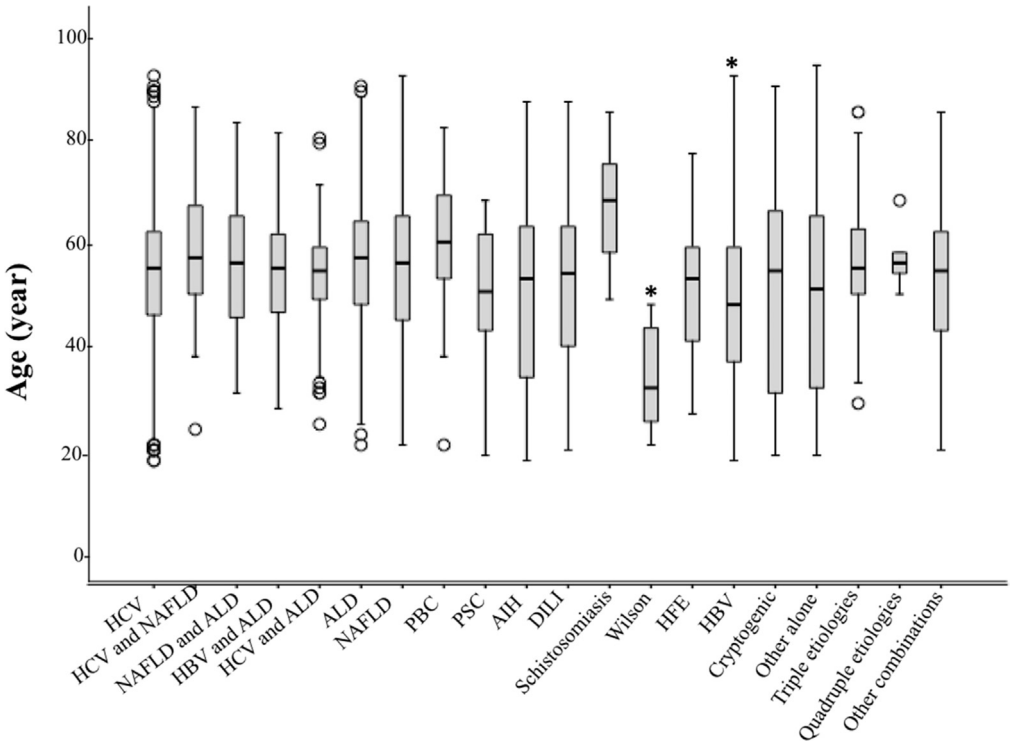
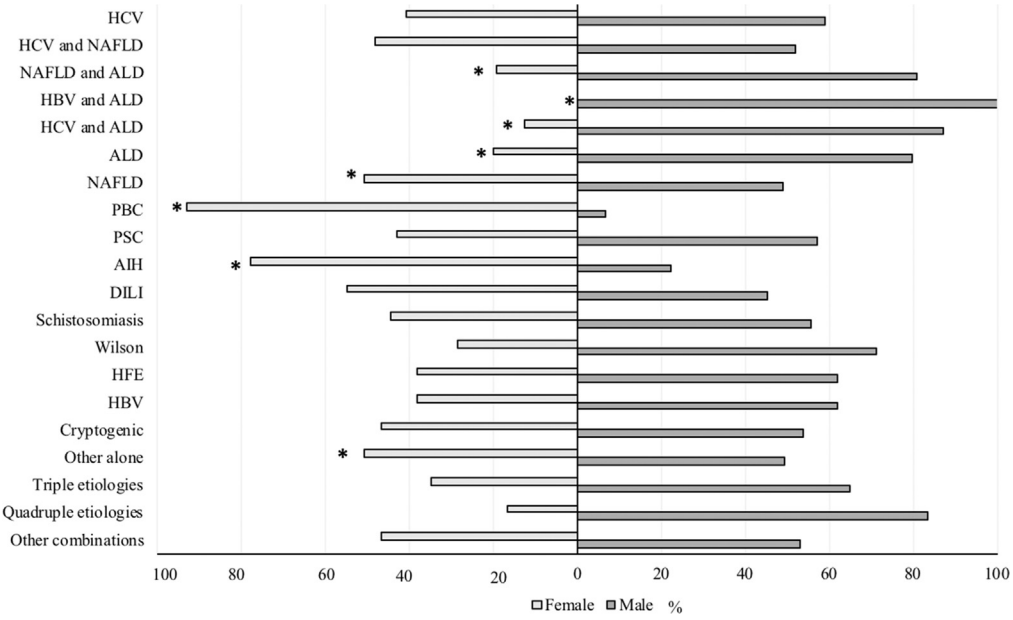


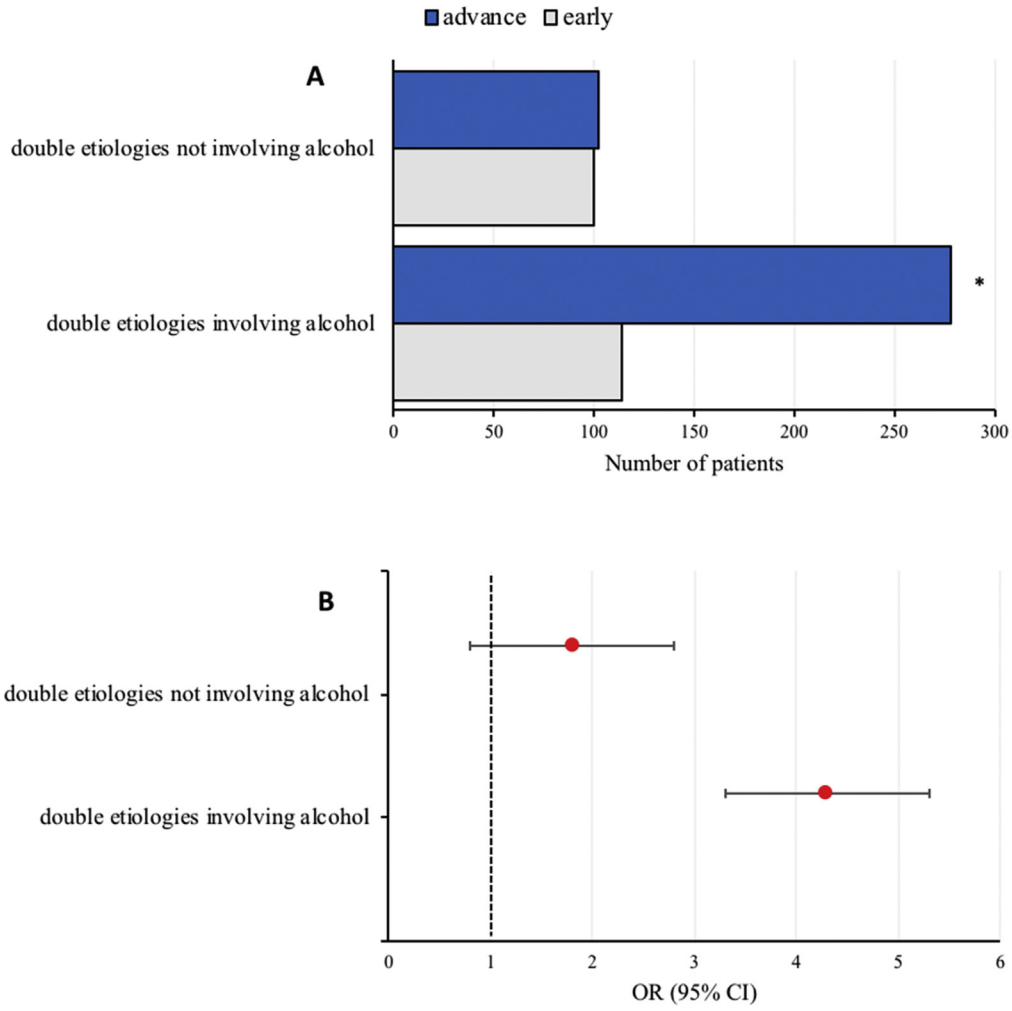
Supplementary Figure 1. The participating countries and centers were as follows: Argentina: Department of Gastroenterology and Hepatology from the University of Rosario School of Medicine, Rosario; Australia: Storr Liver Centre, Westmead Millennium Institute and Westmead Hospital, University of Sydney, Westmead, New South Wales; Bosnia and Herzegovina: Department of Hepatology, Institute of Gastroenterology, Clinical Center of Sarajevo University, Sarajevo (only 99 early patients were included by this center); Brazil: Department of Gastroenterology, University of São Paulo School of Medicine, São Paulo; China: Division of Gastroenterology, Union Hospital, Huazhong University of Science and Technology, Wuhan; Cuba: Department of Hepatology, Instituto de Gastroenterología, Habana; Egypt: Department of Internal Medicine, Al-Azhar University, Cairo; Germany: Department of Gastroenterology, Hamburg University Medical Center, Hamburg; India: Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh; Kenya: Department of Medicine, School of Medicine, College of Health Sciences, Moi University, Eldoret, Kenya; Kuwait: Haya Al-Habeeb Gastroenterology Center, Mubarak Al-Kabeer Hospital, Jabriya; Portugal: Departmento de Gastrenterologia e Hepatologia, Centro Hospitalar Lisboa Norte, Laboratório de Nutrição, Faculdade de Medicina, Universidade de Lisboa, Lisboa; Russia: Department of Gastroenterology and Hepatology, Federal Research Center for Nutrition, Biotechnology and Food Safety, Moscow (Russia has 2 types of centers: alcohol-specialized centers and nonalcohol-specialized centers, both centers belong to the same hospital system. Patients with alcoholic liver disease in either early or advanced stages are seen in alcohol-specialized centers. Because of this idiosyncrasy, we decided on a time period stratagem. All of the Russian patients seen in the nonalcohol-specialized center during a 40-day $\pm$ 7-day period of time were included (early, n $=$ 87; advanced, n $=$ 88); the same time frame was used in the alcohol-specialized center (early, n $=$ 13; advanced, n $=$ 66); Singapore: Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore; South Korea: Department of Internal Medicine, Division of Gastroenterology and Hepatology, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul; Spain: Gastroenterology Department, Liver Unit, Hospital Universitario de Burgos, Burgos; United States: Division of Gastroenterology and Hepatology, Departments of Medicine and Nutrition, University of North Carolina at Chapel Hill, North Carolina. All the hospitals are tertiary care centers. They are either the only referral hospital or at least one of the main referral hospitals for their geographic area. Only public hospitals or hospitals that accepted both insured and uninsured patients were allowed in the study.



Supplementary Figure 2. Age distribution by etiology. Age distribution and differences compared with patients with hepatitis C (reference category). *$P < .05$. AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; HFE, hemochromatosis; NAFLD; nonalcoholic liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.



Supplementary Figure 3. Sex distribution by etiology. Sex distribution and differences compared with patients with hepatitis C (reference category). *$P < .05$. We have not performed the statistics when the frequency for each sex was fewer than 5 cases (ie, Wilson disease, schistosomiasis, and quadruple etiologies). AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; HFE, hemochromatosis; NAFLD; nonalcoholic liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.



Supplementary Figure 4. Double etiologies by liver stage and odds ratio of advanced vs early liver stage. (*A*) Double etiologies patients by liver stage. (*B*) Odds ratio (OR) of being seen at advanced stage vs early liver disease stages. Patients with more than 2 etiologies were excluded in this analysis. The OR of being visited at advanced stage vs early liver disease stages compared with patients with hepatitis C (reference category). *$P < .05$.

Supplementary Table 1. Diagnostic Criteria Used to Define Disease Etiologies

Etiology	Diagnostic criteria
HBV	DNA or HBsAg positive
HCV	HCV RNA positive by a sensitive molecular method (lower limit of detection, 615 IU/mL)
ALD	Alcohol consumption ≥60 g/d men, ≥40 g/d women for at least 6 mo
	Compatible clinical, analytical, imaging, or histologic findings
	BMI < 30
NAFLD	Compatible clinical, analytical, imaging, or histologic findings
	BMI > 35 and/or presence of diabetes, hypertriglyceridemia, or hypercholesterolemia
	Exclusion of both secondary causes and of a daily alcohol consumption of 30 g for men and 20 g for women
Cryptogenic	Unclear cause of liver disease after performing physical exploration and extensive laboratory, imaging, and histologic evaluation
HFE	C282Y homozygosity with increased iron stores
	C282Y/H63D compound heterozygotes and H63D homozygotes presenting with increased serum ferritin levels (>200 mg/L in females, >300 mg/L in males), increased transferrin saturation (>45% in females, >50% in males), and rule out other causes of hyperferritinemia
	Genetic testing of other hemochromatosis genes (TFR2, SLC40A1, HAMP, HJV) could be considered in patients with increased iron stores after exclusion of C282Y homozygosity if iron excess has been proven by direct assessment (ie, by MRI or liver biopsy), and other hepatic and hematologic disorders have been ruled out
Autoimmune	Positive antibodies and analytical and imaging features and/or histologic confirmation
	A score of ≥7 in the simplified diagnostic criteria of the International Autoimmune Hepatitis Group[1]
Wilson disease	Kayser–Fleischer ring and low serum ceruloplasmin (<0.1 g/L)
	Wilson disease scoring system ≥4[2]
DILI	History of recent exposure to a known hepatotoxic agent
	Diagnosis of exclusion based primarily on a detailed history of blood tests, hepatobiliary imaging, and liver biopsy
PBC	Cholestasis, increased ALP level, and the presence of AMA at a titer >1:40 and compatible clinical and analytical picture and/or histologic confirmation
	AMA negative PBC: diagnosis can be made in patients with cholestasis and specific ANA immunofluorescence (nuclear dots or perinuclear rims) or ELISA results (sp100, gp210)
	Biopsy-proven
PSC	Compatible clinical, analytical, and imaging features and/or histologic confirmation
	Other cholestatic disorders excluded
Other	Other causes of liver disease that do not fit in the previous categories

NOTE. Patients were allowed to have 2 or more potential etiologies of liver disease. We decided to group the patients in the most common existent double etiologies: HCV and ALD, HBV and ALD, HCV and NAFLD, and NAFLD and ALD; we thought that it was important to introduce this last category in the study. Although controversial and not yet fully well characterized, there is a current effort to develop a new nomenclature for patients with a combined etiology (ie, dual-etiology fatty liver disease).

ALD, alcoholic liver disease; ALP, Alkaline phosphatase; AMA, antimitochondrial antibody; ANA, Antinuclear antibodies; BMI, body mass index; DILI, drug-induced liver injury; ELISA, enzyme-linked immunosorbent assay; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HFE, hemochromatosis; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

Supplementary Table 2. Odds Ratio of Visits to a Liver/GI Specialist Center at Advanced Stages of the Disease by Etiology

	Total number of patients n = 3453	Bivariable analysis		Multivariable analysis[a]	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, *y*					
≤40	677	0.22 (0.18–0.27)	<.001	0.2 (0.16–0.25)	<.001
41–50	669	0.47 (0.39–0.56)	<.001	0.38 (0.31–0.47)	<.001
>50	2107	1 (reference)		1 (reference)	
Sex					
Female	1344	0.61 (0.53–0.7)	<.001	0.81 (0.68–0.95)	.011
Male	2109	1 (reference)		1 (reference)	
Etiologies					
ALD	573	14.1 (10.5–18.9)	<.001	15.3 (11.3–20.9)	<.001
HBV	523	0.78 (0.62–0.99)	.004	1 (0.79–1.3)	.9
NAFLD	407	0.74 (0.57–0.96)	.02	0.74 (0.57–0.97)	<.001
Cryptogenic	148	3.5 (2.4–5)	<.001	4.9 (3.2–7.2)	<.001
AIH	117	1.5 (0.99–2.7)	.06	2 (1.3–3.1)	.001
PBC	45	0.72 (0.37–1.4)	.3	0.65 (0.33–1.3)	.2
PSC	28	1.8 (0.83–3.8)	.14	2.2 (0.98–4.8)	.06
DILI	31	1.1 (0.5–2.3)	.8	1.3 (0.6–2.9)	.5
HFE	21	0.09 (0.01–0.66)	.018	0.09 (0.01–0.64)	.02
Other alone	59	2.2 (1.3–3.8)	.003	3.3 (1.8–5.9)	<.001
HCV and ALD	134	5.6 (3.7–8.6)	<.001	5.6 (3.5–8.5)	<.001
HBV and ALD	47	6.5 (3.2–13.3)	<.001	7.7 (3.6–16.1)	<.001
NAFLD and ALD	104	5 (3.2–7.9)	<.001	5.6 (3.4–9.1)	<.001
Other combinations	228	2.1 (1.5–2.8)	<.001	2.5 (1.8–3.4)	<.001
HCV and NAFLD	81	1.72 (1.1–2.7)	.02	1.6 (0.98–2.5)	.65
Triple etiologies	60	7.88 (4–15.4)	<.001	8.2 (4.1–16.3)	<.001
Quadruple etiologies	6	8.8 (1–76)	.05	6.9 (0.79–61)	.08
HCV	825	1 (reference)		1 (reference)	

AIH, autoimmune hepatitis; ALD, alcoholic liver disease; DILI, drug-induced liver injury; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; HFE, hemochromatosis; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.
[a]Multivariate analysis included age, sex and etiology.

Supplementary Table 3. Etiology of Liver Disease by Continent and Disease Stage

	Africa		America		Asia		Europe		Oceania	
	400		800		1000		1053		400	
Etiology, n (%)	Early	Advanced	Early	Advanced	Early	Advanced	Early	Advanced	Early	Advanced
HCV	73 (18.3)	67 (16.8)	133 (16.6)	71 (8.9)[a]	148 (14.8)	100 (10)[a]	149 (14.2)	56 (5.3)[a]	24 (12)	4 (2)[a]
HBV	34 (8.5)	22 (5.5)	69 (8.6)	21 (2.6)[a]	135 (13.5)	89 (8.9)[a]	93 (8.8)	21 (2)[a]	31 (15.5)	8 (4)[a]
ALD	27 (6.8)	48 (12)[a]	8 (1)	102 (12.8)[a]	19 (1.9)	133 (13.3)[a]	9 (0.8)	175 (16.6)[a]	1 (0.5)	51 (25.5)[a]
NAFLD	6 (1.5)	2 (0.5)	49 (6.1)	52 (6.5)	141 (14.1)	41 (4.1)[a]	77 (7.3)	18 (1.7)[a]	14 (7)	7 (3.5)
Cryptogenic	38 (9.5)	22 (5.5)[a]	0	9 (1.1)[a]	5 (0.5)	31 (3.1)[a]	7 (0.6)	35 (3.3)[a]	0	1 (0.5)
AIH	4 (1)	5 (1.3)	29 (3.6)	18 (2.3)	10 (1)	13 (1.3)	18 (1.7)	15 (1.4)	3 (1.5)	2 (1)
PBC	0	0	13 (1.6)	8 (1)	1 (0.1)	0	17 (1.6)	5 (0.4)[a]	1 (0.5)	0
PSC	0	0	3 (0.4)	4 (0.5)	3 (0.3)	0	8 (0.7)	10 (0.9)	0	0
DILI	2 (0.5)	5 (1.2)	8 (1)	3 (0.4)	2 (0.2)	2 (0.2)	5 (0.3)	2 (<0.1)	2 (1)	0
Other[b]	6 (1.5)	7 (1.8)	8 (1)	21 (2.6)[a]	5 (0.5)	17 (1.7)[a]	33 (3.1)	49 (4.7)	14 (7)	2 (1)[a]
Double etiologies not involving ALD	4 (1)	15 (3.8)[a]	25 (3.1)	18 (2.3)	16 (1.6)	28 (2.8)	50 (4.7)	41 (3.8)	5 (2.5)	0
Double etiologies involving ALD	6 (1.5)	7 (1.8)	55 (6.9)	73 (9.1)	15 (1.5)	46 (4.6)[a]	33 (3.1)	127 (12)[a]	5 (2.5)	25 (12.5)[a]

NOTE. Number of patients included by continent.

AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

[a]$P < .05$.

[b]Because of their low global frequency, Wilson disease, hemochromatosis, schistosomiasis, and triple or quadruple etiologies were included in the category of *other*.

Supplementary Table 4. Odds Ratio and 95% CI of Advanced Vs Early Liver Disease Visits by Continent

Africa	Total number of patients n = 400[b]	Bivariable analysis		Multivariable analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, *y*					
≤40	143	0.36 (0.22–0.57)	<.001	0.37 (0.22–0.61)	<.001
41–50	84	0.71 (0.42–1.2)	<.2	0.68 (0.39–1.2)	.2
>50	173	1 (reference)		1 (reference)	
Sex					
Female	158	0.58 (0.39–0.87)	<.008	0.65 (0.42–1)	.06
Male	242	1 (reference)		1 (reference)	
Etiologies					
ALD	75	1.9 (1.1–3.4)	.03	2.3 (1.3–4.3)	.007
HBV	56	0.71 (0.38–1.3)	.3	1 (0.53–2.1)	.9
NAFLD	8	0.36 (0.07–1.9)	.2	0.42 (0.08–2.2)	.3
Cryptogenic	60	0.63 (0.34–1.2)	.1	0.99 (0.51–1.9)	1
AIH	9	1.4 (0.35–5.3)	.7	2.3 (0.6–9.3)	.3
PBC	—	—		—	
PSC	—	—		—	
DILI	7	2.7 (0.51–14.5)	.2	3.2 (0.56–18)	.2
HFE	—	—		—	
Other alone	10	2.5 (0.63–10.2)	.2	2.9 (0.7–12.7)	.1
Double etiologies not involving OH	19	4.1 (1.3–12.9)	.02	3.8 (1.2–12.4)	.03
Double etiologies involving OH	13	1.3 (0.41–3.9)	.6	1.3 (0.9–4)	.7
HCV	140	1 (reference)		1 (reference)	
Asia	Total number of patients n = 1000[a]			Multivariable analysis[b]	
Age, *y*					
≤40	213	0.14 (0.1–0.2)	<.001	0.1 (0.07–0.16)	<.001
41–50	203	0.35 (0.25–0.48)	<.001	0.23 (0.15–0.34)	<.001
>50	584	1 (reference)		1 (reference)	
Sex					
Female	274	0.63 (0.47–0.83)	<.001	0.8 (0.59–1.2)	.3
Male	421	1 (reference)		1 (reference)	
Etiologies					
ALD	152	10.3 (6–17.8)	<.001	13.5 (7.4–24.5)	<.001
HBV	224	0.9 (0.68–1.4)	.9	1.1 (0.75–1.7)	.6
NAFLD	182	0.4 (0.28–0.66)	<.001	0.37 (0.23–0.6)	.3
Cryptogenic	36	9.2 (3.5–24.4)	<.001	6.9 (2.4–19.7)	<.001
AIH	23	1.9 (0.8–4.6)	.13	1.6 (0.63–4.2)	.3
PBC	1	—		—	
PSC	3	—		—	
DILI	4	1.4 (0.2–10.7)	.7	1.1 (0.13–8.4)	1
HFE	—	—		—	
Other alone	10	3.5 (0.87–13.7)	.08	11.9 (2.7–52)	.001
Double etiologies not involving OH	44	2.6 (1.3–5)	.005	2.7 (1.3–5.5)	.009
Double etiologies involving OH	61	4.5 (2.4–8.6)	<.001		
HCV	248	1 (reference)		1 (reference)	
America	Total number of patients n = 800[a]				
Age, y					
≤40	123	0.29 (0.19–0.45)	<.001	0.33 (0.2–0.55)	<.001
41–50	127	0.61 (0.41–0.9)	.013	0.56 (0.36–0.87)	.01
>50	550	1 (reference)		1 (reference)	
Sex					
Female	386	0.58 (0.44–0.9)	<.001	0.81 (0.58–1.1)	.2
Male	413	1 (reference)		1 (reference)	
Etiologies					
ALD	110	23.8 (11–51)	<.001	25.5 (11.7–55.8)	<.001
HBV	90	0.57 (0.3–1)	.05	0.75 (0.42–1.3)	.3
NAFLD	101	1.99 (1.2–3.2)	.005	2.1 (1.3–3.4)	.004
Cryptogenic	9	—		—	
AIH	47	1.2 (0.6–2.2)	.6	1.7 (0.86–3.5)	.1

Supplementary Table 4. Continued

Africa	Total number of patients n = 400[b]	Bivariable analysis		Multivariable analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
PBC	21	1.2 (0.46–2.9)	.8	1.1 (0.44–2.8)	.8
PSC	7	2.49 (0.54–11.5)	.2	2.9 (0.63–14)	.2
DILI	11	0.7 (0.18–2.7)	.6	0.94 (0.23–3.8)	.9
HFE	4	0.64 (0.06–6.1)	.7	0.69 (0.07–6.9)	.8
Other alone	13	6.2 (1.7–23)	.007	8.3 (2.1–32.6)	.002
Double etiologies not involving OH	43	1.3 (0.69–2.6)	.4	1.5 (0.8–3)	.2
Double etiologies involving OH	128	2.5 (1.6–3.9)	<.001	2.6 (1.6–4.1)	<.001
HCV	204	1 (reference)		1 (reference)	
Europe	**Total number of patients n = 1053[a]**				
Age, *y*					
≤40	166	0.21 (0.15–0.32)	<.001	0.23 (0.14–0.36)	<.001
41–50	214	0.39 (0.28–0.53)	<.001	0.38 (0.25–0.57)	<.001
>50	673	1 (reference)		1 (reference)	
Sex					
Female	442	0.68 (0.53–0.87)	.002	1.2 (0.84–1.6)	.4
Male	611	1 (reference)		1 (reference)	
Etiologies					
ALD	184	51.7 (24.8–108)	<.001	49.8 (23.5–105)	<.001
HBV	114	0.6 (0.3–1.1)	.008	0.69 (0.39–1.2)	.02
NAFLD	95	0.62 (0.34–1.3)	.1	0.62 (0.34–1.1)	.1
Cryptogenic	42	13 (5.6–31.6)	<.001	16.8 (6.7–41.8)	<.001
AIH	33	2.2 (1–4.7)	.04	2.3 (1.1–5)	.04
PBC	22	0.78 (0.27–2.2)	.7	0.63 (0.22–1.8)	.4
PSC	18	3.3 (1.2–8.9)	.23	3.8 (1.4–10.6)	.01
DILI	7	1.1 (0.2–5.6)	.9	1.4 (0.24–8.1)	.7
HFE	15	—		—	
Other alone	12	3.7 (1.1–12.2)	.03	4.1 (1.2–14.3)	.03
Double etiologies not involving OH	91	2.2 (1.3–3.7)	.003	2.7 (1.6–4.6)	<.001
Double etiologies involving OH	160	10.3 (6.3–16.7)	<.001	11.2 (6.7–18.7)	<.001
HCV	205	1 (reference)		1 (reference)	
Oceania	**Total number of patients n = 200[a]**				
Age, *y*					
≤40	32	0.04 (0.01–0.19)	.3	0.08 (0.02–4.7)	.005
41–50	41	0.68 (0.34–1.4)	.3	0.52 (0.17–1.5)	.2
>50	127	1 (reference)		1 (reference)	
Sex					
Female	79	0.39 (0.21–0.75)	.005	0.82 (0.32–2.1)	.7
Male	121	1 (reference)		1 (reference)	
Etiologies					
ALD	52	306 (32–2886)	<.001	279 (28.9–2703)	<.001
HBV	39	1.5 (0.42–5.8)	.5	2.7 (0.65–11.4)	.2
NAFLD	21	3 (0.74–12.1)	.1	2.6 (0.63–10.7)	.2
Cryptogenic	1	—		—	
AIH	5	4 (0.5–31)	.1	9.5 (0.9–102)	.06
PBC	1	—		—	
PSC	—	—		—	
DILI	2	—		—	
HFE	2	—		—	
Other alone	14	1 (0.6–6.3)	1	1.6 (0.23–10.8)	.6
Double etiologies not involving OH	5	—		—	
Double etiologies involving OH	14	30 (7.2–125)	<.001	36 (7.9–165)	<.001
HCV	28	1 (reference)		1 (reference)	

AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; OH, Alcohol; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

[a]In Africa, 1 patient with schistosomiasis, 1 patient with Wilson disease, and 1 patient with triple etiologies are not represented in the table; in Asia, 6 patients with triple etiologies, 1 patient with quadruple etiologies, 1 with Wilson disease and 4 with schistosomiasis are not represented in the table; in Europe, 5 patients with Wilson disease, 45 patients with triple etiologies, and 5 patients with quadruple etiologies are not represented in the table; in America, 4 patients with schistosomiasis and 8 patients with triple etiologies are not represented in the table.

[b]Multivariate analysis included age, sex, and etiology.

Supplementary Table 5. Breakdown of the Etiology of Liver Disease in Asian Countries by Liver Stage

	Asia (all)		Kuwait		China	
	1000		200		200	
Etiology, n (%)	Early	Advanced	Early	Advanced	Early	Advanced
HCV	148 (14.8)	100 (10)[a]	58 (29)	47 (23.5)	1 (0.5)	6 (3)
HBV	135 (13.5)	89 (8.9)[a]	24 (12)	6 (3)[a]	28 (14)	33 (16.5)
ALD	19 (1.9)	133 (13.3)[a]	0	7 (3.5)[a]	9 (4.5)	12 (6)
NAFLD	141 (14.1)	41 (4.1)[a]	6 (0.3)	19 (9.5)[a]	46 (23)	6 (3)[a]
Cryptogenic	5 (0.5)	31 (3.1)[a]	1 (0.5)	11 (5.5)[a]	1 (0.5)	0
AIH	10 (1)	13 (1.3)	3 (1.5)	2 (1)	4 (2)	8 (4)
PBC	1 (0.1)	0	0	0	1 (0.5)	0
PSC	3 (0.3)	0	3 (1.5)	0	0	0
DILI	2 (0.2)	2 (0.2)	0	0	0	2 (1)
Other[b]	5 (0.5)	17 (1.7)[a]	3 (1.5)	2 (1)	1 (0.5)	9 (4.5)[a]
Double etiologies not involving ALD	16 (1.6)	28 (2.8)	2 (1)	6 (3)	4 (2)	11 (5.5)
Double etiologies involving ALD	15 (1.5)	46 (4.6)[a]	0	0	5 (2.5)	13 (6.5)

	South Korea		Singapore			
	200		200		India	
HCV	9 (4.5)	18 (9)	29 (14.5)	24 (12)	51 (25.5)	5 (2.5)[a]
HBV	28 (14)	25 (12.5)	34 (17)	19 (9.5)[a]	21 (10.5)	6 (3)[a]
ALD	9 (4.5)	36 (18)[a]	1 (0.5)	17 (8.5)[a]	0	61(30.5)[a]
NAFLD	47 (23.5)	1 (0.5)[a]	24 (12)	13 (6.5)	18 (9)	2 (1)[a]
Cryptogenic	2 (1)	9 (4.5)	1 (0.5)	9 (4.5)[a]	0	2 (1)
AIH	3 (1.5)	0	0	3 (1.5)	0	0
PBC	0	0	0	0	0	0
PSC	0	0	0	0	0	0
DILI	2 (1)	0	0	0	0	0
Other[b]	0	1 (0.5)	1 (0.5)	0	0	5 (2.5)
Double etiologies not involving ALD	0	0	6 (3)	5 (2.5)	4 (2)	6 (3)

AIH, autoimmune hepatitis; ALD, alcohol-related liver disease; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

[b]Because of their low global frequency Wilson disease, hemochromatosis, schistosomiasis, and triple or quadruple etiologies were included in the category of *other*.

Supplementary Table 6. Sex and Age Differences in Advanced Vs Early Visits for ALD Patients

		Bivariable analysis		Multivariable analysis[a]	
	ALD patients n = 573	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, *y*					
≤40	59	0.26 (0.13–0.53)	<.001	0.26 (0.13–0.53)	<.001
41–50	126	0.4 (0.22–0.74)	.003	0.4 (0.22–0.73)	.003
>50	388	1 (reference)		1 (reference)	
Sex					
Female	116	0.99 (0.52–1.9)	.99	1.1 (0.55–1.9)	.89
Male	457	1 (reference)		1 (reference)	

ALD, alcohol-related liver disease; OR, odds ratio.
[a]Multivariate analysis included age, sex, and etiology. When compared with patients older than age 50, the other 2 age groups (≤40 y and 41–50 y), presented with a lower OR for being seen at specialized centers during advanced disease stages. No significant difference was observed between female and male populations.

Supplementary Table 7. Race, Sex, and Age Differences in Advanced Vs Early Visits for Patients With Double Etiologies Involving Alcohol

		Bivariable analysis		Multivariable analysis[a]	
	Double etiologies involving OH, n = 392	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, *y*					
≤40	43	0.36 (0.18–0.71)	.003	0.36 (0.19–0.71)	.003
41–50	87	0.57 (0.34–0.96)	.036	0.54 (0.32–0.91)	.002
>50	262	1 (reference)			
Sex					
Female	83	0.66 (0.39–1.1)	.11	0.62 (0.36–1)	.07
Male	309	1 (reference)			

OH, Alcohol; OR, odds ratio.
[a]Multivariate analysis included age, sex, and etiology.

Supplementary Table 8. Sex, Age, and Race in the United States: Differences in Advanced Vs Early Visits for Any Etiology

	Bivariable analysis		Multivariable analysis[a]	
	US patients, n = 200	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, y					
≤40	19	0.57 (0.21–1.5)	.3	0.26 (0.13–0.53)	<.001
41–50	25	1.2 (0.53–2.9)	.6	1.3 (0.53–3.1)	.6
>50	156	1 (reference)		1 (reference)	
Sex					
Female	88	0.67 (0.38–1.2)	.2	0.63 (0.36–1.1)	.1
Male	112	1 (reference)		1 (reference)	
Race					
Hispanic	10	1.3 (0.34–4.7)	.7	1.2 (0.33–4.6)	.8
Black	43	0.5 (0.24–1)	.052	0.48 (0.24–0.97)	.04
Asian	3	0.42 (0.04–4.7)	.4	0.39 (0.03–4.5)	.5
Middle Eastern	—	—		—	
Indian	1	—		—	
Indeterminate[b]	—	—		—	
Other	3	0.42 (0.04–4.7)	.4	0.34 (0.03–3.9)	.4
White	140	1 (reference)		1 (reference)	

NOTE. Because of the lack of a homogeneous race and gender distribution, no conclusion could be reached regarding race differences.
OR, odds ratio.
[a]Multivariate analysis included age, sex and etiology.
[b]Indeterminate race or ethnicity including mixed race population.

Supplementary Table 9. Sex, Age, and Race in the United States: Differences in Advanced Vs Early Visits for Patients With ALD as a Single Diagnoses or Double Etiologies Involving OH

	Bivariable analysis		Multivariable analysis[a]		
	ALD patients n = 80	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, *y*					
≤40	7	0.54 (0.1–2.7)	1	0.56 (0.1–2.9)	.5
41–50	14	1 (0.28–3.7)	.003	1.1 (0.29–3.0)	.9
>50	59	1 (reference)		1 (reference)	
Sex					
Female	31	0.66 (0.25–1.7)	.4	0.69 (0.26–1.8)	.6
Male	49	1 (reference)		1 (reference)	
Race					
Hispanic	2	—	—	—	—
Black	15	0.61 (0.19–1.9)	.4	0.61 (0.19–1.9)	.4
Asian	1	—	—	—	—
Middle Eastern	—	—	—	—	—
Indian	—	—	—	—	—
Indeterminate[b]	—	—	—	—	—
Other	—	—	—	—	—
White	62	1 (reference)		1 (reference)	

ALD, alcohol-related liver disease; OH, Alcohol; OR, odds ratio.
[a]Multivariate analysis include sex, age and etiology.
[b]Indeterminate race or ethnicity including mixed race population.